Regulatory Paradigms for Modern Breeding

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Modern breeding, based upon molecular biology using genetic information, has made rapid advances. Breeders using rDNA techniques can properly think of this technique as traditional biotechnology. Within the past ten years, breeders have begun to use newer techniques [site-directed nuclease techniques (SDNs), RNAi, and synthetic biology] to create and to develop plants and animals with desired genetic traits.

Traditional breeding, whether by farmers or by scientists, has been either unregulated or lightly regulated, primarily to assure seed purity and efficacy. The rDNA techniques have been carefully regulated domestically and internationally. The regulatory classifications of the newer techniques of the past ten years are still in debate and have much uncertainty.

In this chapter, the authors address the question: What is an appropriate regulatory paradigm for modern breeding?

At the Beginning

Questions about the appropriate regulatory paradigm for modern breeding emerged concurrently with the breeding techniques themselves—specifically rDNA breeding. It is very helpful and instructive to read anew the conclusions reached at the beginning of rDNA breeding.

The US National Academy of Science (NAS, 1987) concluded: "There is no evidence that unique hazards exist either in the use of R-DNA techniques or in the movement of genes between unrelated organisms." And further, "Assessment of the risks of introducing R-DNA engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced."

The US Office of Science and Technology Policy (OSTP, 1992) wrote, "Exercise of oversight in the scope of discretion afforded by statute should be based on the risk posed by the introduction and should not turn on the fact that an organism has been modified by a particular process or technique. ... [O]versight will be exercised only where the risk posed by the introduction is unreasonable, that is, when the value of the reduction in risk obtained by additional oversight is greater than the cost thereby imposed."

Similarly, the Organisation for Economic Co-Operation and Development (OECD, 1986) recommended:

> *2. There is no scientific basis for specific legislation for the implementation of rDNA techniques and applications. Member countries should examine their existing oversight and review mechanisms to ensure that adequate review and control may be applied while avoiding any undue burdens that may hamper technological development in this field.*
>
> *3. Any approach to implementing guidelines should not impede future developments in rDNA techniques. International harmonization should recognise this need.*
>
> *6. .... For certain industrial applications and for environmental and agricultural applications of rDNA organisms, countries may wish to have a notification scheme.*

The regulatory paradigm recommended in the three quoted documents urged a focus on the organism (product) and not the process of breeding, while understanding that the empirical evidence does not show any unique hazards, and proposed the use of general legislation with the OECD suggesting an amendment limited to requiring a notification scheme. It is evident that NAS, OSTP, and OECD concluded that modern breeding should be regulated like traditional breeding—*i.e.* unregulated or lightly regulated.

The Regulatory Reality

The United States did not adopt biotechnology-specific legislation. Rather, the US government developed a coordinated framework (OSTP, 1986) allowing the three primary administrative agencies [Department of Agriculture (USDA), Environmental Protection Agency (EPA), and Food and Drug Administration (FDA)] to develop policies under existing statutory authorities about regulating rDNA techniques.

The USDA Animal Plant Health Inspection Service (APHIS) created a category called a "regulated article" under the Plant Protection Act. EPA created a category called a "plant-incorporated protectant" (PIP) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FDA created a voluntary consultation process for foods derived from biotechnology and later declared that all animals derived from biotechnology are "new drugs" using the Federal Food Drug & Cosmetic Act (FDA, 2009). What each of these regulatory approaches have in common is that these newly created categories captured rDNA breeding as the trigger for extensive regulation. Extensive regulation means an application process requiring much data and regulatory filings, public comments and hearings, and prior approval (permission) from the agency before any biotechnological

product can enter the market. No other breeding techniques (or their crop and animal offspring) face anything close to this level of regulatory scrutiny[1].

Beginning in 1990, the European Union (EU) enacted a series of biotechnology-specific directives and regulations. In 1998, after the "mad-cow" events, the EU undertook revision of the 1990 laws, culminating in three of particular applicability to agricultural biotechnology: directive 2001/18/EC (on the deliberate release into the environment of GMOs), regulation 1829/2003 (on GM food and feed), and regulation 1830/2003 (on the traceability and labeling of GMOs and the traceability of food and feed products produced from GMOs). The EU directives and regulations focused specifically on the process by which a product came into existence and enmeshed these processes and products in extensive risk analyses related to health and environmental concerns (EU, 2013).

New Zealand enacted biotechnology-specific legislation titled "The Hazardous Substances and New Organisms (HSNO) Act of 1996." By associating biotechnology with hazardous substances, New Zealand created extensive regulatory scrutiny just for agricultural biotechnology.

At the international level, 168 countries have ratified the Cartagena Protocol on Biosafety governing the transboundary movement of "living modified organisms" from "modern biotechnology." Although the Cartagena Protocol is a very complicated and intricate document, it is fair to say that it created and continues to create extensive regulatory controls over the international trade in crops and animals from agricultural biotechnology.

The EU, New Zealand, and Cartagena Protocol all share several features: a focus on process, not product; detailed and rigorous risk analyses without requiring evidence of any unreasonable risks or unique hazards; prior approval before commercial use that is subject to political influences; and a plodding decision-making process. Moreover, each of these three regulatory approaches explicitly adopts a precautionary stance towards agricultural biotechnology, implicitly communicating through laws or regulations that society should "[b]e afraid, be very afraid of agricultural biotechnology."

Surveying the regulatory reality, it becomes clear that agricultural biotechnology faces extensive regulation wherever created or located. Governments and agencies around the world have not adopted the regulatory paradigm recommended by NAS, OSTP, and OECD. Just the opposite, governments and agencies have adopted a regulatory paradigm that expressly and purposefully burdens agricultural biotechnology. In light of these regulatory burdens, one can be amazed that a few products of agricultural biotechnology have achieved the level of adoption that the International Service for the Acquisition of Agri-Biotech Applications annually reports (ISAAA, 2014).

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[1]The FDA voluntary consultation process uses the concept of "comparative safety analysis," sometimes known as substantial equivalence, whereby foods derived from biotechnology considered substantially equivalent to comparable conventional foods, in that they lack any novel substances that can cause harm, can enter the market without FDA prior approval. No developer of biotech-food products has been sufficiently courageous or foolhardy to interpret the "voluntary" consultation process as embodying the phrase, "It is better to ask forgiveness than permission." The FDA voluntary consultation process has verified the safety of food, and FDA has responded in a timely manner without excessive burdens or barriers to foods from crop biotechnology.

Past and Present Impact of the Regulatory Reality

What has been the impact of these excessive and stigmatizing regulations upon agricultural biotechnology?

- USDA-APHIS has approved 96 petitions for non-regulated status. Farmers have adopted these approved (and improved) traits immediately and widely. For corn, soybean, canola, sugarbeet, and cotton, farmers have adopted GM varieties at 90 percent or above of acres planted (Fernandez-Cornejo, 2014). Yet, USDA-APHIS now takes nearly 5 years to make a decision with a regulatory cost per trait up to $34 million.

  The impact of this cumbersome, expensive, and labor-intensive process has been stultifying to research and competition. Despite many successful and needed crop transformations by public-sector scientists, only one public-sector crop has ever achieved regulatory approval and commercial release—the virus-resistant papaya for Hawaii. APHIS has also approved a USDA-ARS virus-resistant plum, but EPA pesticide-labeling requirements have prevented its commercial release.
- In 1997, EPA defined genetically-modified microorganisms (GMMs) as regulated "new chemicals" under the Toxic Substances Control Act (TSCA). Since then, EPA has approved one GMM for commercial use.
- FDA has not approved a single commercial release of animal agricultural biotechnology. In possibly the most egregious example, a genetically-engineered fast-growing salmon from AquaBounty, using a Pacific (Chinook) salmon gene transferred to an Atlantic salmon, has been in the regulatory system for almost 20 years with costs above $78 million. FDA has fully cleared the salmon as safe for food and having no, or minimal, risk to the environment. Despite the findings, FDA has not issued a decision, giving rise to a petition letter, initiated by scientists, bemoaning the delay, cost, and suspected political interference (Letter, 2014).
- The EU, in 25 years of its biotechnology-specific regulatory system, has approved only two traits for commercial release to European farmers. Several dozen crop traits have been approved for import as food and feed, but its own farmers cannot grow what farmers in other countries grow and supply to the EU.
- New Zealand has approved a few confined field trials of genetically-modified traits for plants and animals. However, New Zealand has not approved any broad-scale field trials and has never even considered a petition to approve the commercial release of an agricultural trait derived from biotechnology.
- For most countries signatory to the Cartagena Protocol, the Protocol has proven to be an almost impassable barrier to the growing of genetically-modified crops and animals. The most troubling example of the Protocol's impact has been on Golden Rice, engineered to have precursor beta-carotene, a biofortified public

good to reduce blindness and death from vitamin-A deficiency. Ingo Potrykus, a co-inventor and donor of Golden Rice for humanitarian use, has written clearly and passionately about this regulatory blockage (Potrykus, 2012, 2013).

Forecasting the Future Impact of Regulatory Regimes

The forecasted impact of the present regulatory systems on future agricultural biotechnology ranges from cloudy to devastating. These pessimistic forecasts arise from the fact that newer techniques of molecular breeding—SDNs (such as MNs, ZFNs, TALENs and CRISPRs-Cas9), RNAi, and synthetic biology—have not been classified clearly and explicitly as subject to the existing regulatory regimes or not subject. Uncertainty about regulatory classification serves as a disincentive to engage in research and development and an even greater disincentive to investment in these techniques for commercial release (Smyth, 2014).

The authors have previously analyzed the specific definitions and provisions of regulatory schemes (except for New Zealand) in an attempt to make informed predictions about the application of present regulations to these newer breeding techniques (Kershen and Parrott, 2013). We now present a brief summary of this legal analysis.

USDA-APHIS regulates biotechnology through the Plant Protection Act. Consequently, APHIS focuses on whether the biotechnological technique involves the use of a plant pest at any stage of the genetic engineering. APHIS allows developers to query whether a particular engineered plant is or is not regulated (USDA-APHIS, 2014).

As of September 2014, APHIS has not been queried specifically about TALENS and CRISPRs-Cas9. However, in two letters—one on ZFN-1 and one on MN-1 breeding—APHIS stated that such plants were not subject to regulation because the techniques did not involve use of any plant pest at any stage. In these two letters, APHIS cautioned that SDN-2 and SDN-3 techniques would be dealt with on a situation-by-situation basis.

APHIS also responded to two letters about the Bioglow plants from synthetic biology, concluding that they are outside its regulatory authority because the glowing plants did not involve any plant pest at any stage of their engineering.

Finally, APHIS affirmed that null segregant plants (*i.e.* offspring plants, in which the plant-pest element used to engineer the parent plant has been removed through conventional breeding) are outside its regulatory authority.

In light of these responses to letters of inquiry, USDA-APHIS appears poised to declare many—but not all—plants developed by the newer breeding techniques to be beyond its regulatory authority.

EPA uses FIFRA to regulate plants with traits inserted for the purpose of "preventing, destroying, repelling or mitigating any pest." EPA has asserted FIFRA authority over an RNAi plant created to be virus resistant. Moreover, in a recent scientific advisory panel (SAP) report, the SAP took a very precautionary approach to RNAi breeding and an affirmative view of the need for EPA to assert regulatory authority through FIFRA, including using the FIFRA term "plant regulator" to expand its regulatory reach (FIFRA SAP, 2014).

FDA has asserted that all genetically modified animals are "new animal drugs." FDA appears likely to assert that it will consider any animal modified by these newer breeding techniques also to be "new animal drugs," entailing extensive pre-market scrutiny and approval. FDA's likely regulatory stance is evident in its claim that a "polled" Holstein (dairy) cow, using the "polled gene" from the Angus (beef) breed, created by TALENs, is a "new animal drug" (Regalado, 2014).

As for synthetic biology, the J. Craig Venter Institute released a report in May 2014 setting forth options for regulatory approaches. The minimum option presented was to apply the present regulatory system for rDNA breeding to synthetic biology. All other options proposed enhanced agency power and regulatory scrutiny. The basic message of this Venter report was that nothing in synthetic biology should avoid regulation. Extensive regulation was the default approach (J. Craig Venter Institute, 2014).

The EU has not officially discussed how its extensive regulatory regime on rDNA breeding applies to newer breeding techniques. However, there are several reasons to believe that the EU regulatory system will capture all newer breeding techniques. First, the EU uses a "precautionary principle" as its underlying attitude towards molecular breeding. Extensive regulation is the preferred and default approach. Second, the EU regulations focus specifically on the process, and expressly exempt listed techniques from regulation. The implication appears to be that those not expressly exempted are within the coverage of the regulatory regime. Third, the European Food Safety Authority (EFSA) has opined that the SDN-3 technique does not differ from rDNA breeding (EFSA, 2012). Fourth, the EU regime also covers products of covered techniques, meaning null-segregant plants also would be regulated (EU Working Group, 2013).

In New Zealand, the Environmental Protection Agency (NZ-EPA) decided that ZFN-1 and comparable TALEN techniques were outside the regulatory reach of the HSNO law. The New Zealand Sustainability Council challenged the NZ-EPA decision in a lawsuit. In an opinion issued in May 2014, the High Court (trial court/first level court) of Wellington agreed with the Sustainability Council. The High Court interpreted the statutory list of exempt techniques as exhaustive. As ZFN-1 and TALEN techniques were not expressly exempted, the High Court ruled the HSNO law applied. The High Court stated that the precautionary principle colored its interpretive analysis and opined that the New Zealand Parliament should be the governmental authority to exempt these techniques, not an administrative agency, if doing so is deemed socially desirable (NZ-High Court, 2014).

The Cartagena Protocol on Biosafety has provisions and language that closely resemble the EU and New Zealand regulatory regimes. Thus, it can be predicted that the Cartagena Protocol too is very likely to cover newer breeding techniques as regulated technologies. Moreover, groups antagonistic to rDNA breeding have launched a campaign against the newer breeding techniques, especially synthetic biology, similar to their campaign against rDNA breeding. These groups call for a moratorium on newer breeding techniques until their demands for extensive and stifling regulations exist at all levels of governance—local, federal, and international (FOE, 2013).

Regulatory Paradigms—Proposed Regulatory Reforms

In the United States, rDNA agricultural biotechnology has moved forward in farmers' fields, but at a slow, costly, and halting pace and has not come close to fulfilling its potential mainly because of the impact of excessive regulatory regimes. Despite 30 years of experiences evidencing that agricultural biotechnology has verified the favorable conclusions of NAS, OSTP, and OECD, the US regulatory system has not responded to this real-world evidence of benefits without novel harms. The US regulatory system could be improved through several efforts within the power of the regulatory agencies such as:

- adopting categorical exclusions for those traits that have been already reviewed and proven safe and beneficial;
- focusing anew on product, not process, and on identified unreasonable risk, not imaginable hazards, so as to regulate a particular genetically-engineered crop or animal only if there is a scientific need, not just a default for regulation based on technique used;
- exercising agency discretion to decline invoking new terms and new definitions that expand regulatory power;
- creating a culture of facilitating innovation, science and technology in agriculture to meet the challenges agriculture faces from population growth and climate change.

As for Europe, New Zealand, and the Cartagena Protocol, it is worth quoting from a 2013 report issued by the United Kingdom Advisory Committee on Releases into the Environment (ACRE):

> *Our understanding of genomes does not support a process-based approach to regulation. The continuing adoption of this approach has led to, and will increasingly lead to, problems. This includes problems of consistency,* i.e. *regulating organisms produced by some techniques and not others irrespective of their capacity to cause environmental harm.*
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> *Our conclusion, that the EU's regulatory approach is not fit for purpose for organisms generated by new technologies, also applies to transgenic organisms produced by 'traditional' GM technology. … the potential for inconsistency is inherent because they may be phenotypically identical to organisms that are not regulated* (ACRE, 2013).

The ACRE report provides a bookend that reconfirms what NAS, OSTP, and OECD stated at the beginning. Agricultural biotechnology does not present unique hazards. Regulation should be about the product, not the process. Oversight should occur when the risk posed is unreasonable. There is no need for biotechnology-specific regulatory regimes. Regulation should not hamper and burden scientific discovery and technological adoption.

At the root of a regulatory paradigm is an attitude. In the 1970s and early 1980s, molecular breeding was viewed as new and different from what occured in plants and

conventional breeding. From the genomic perspective, that "new and different" view has long been gone—since the late 1980s as the quoted reports of NAS, NRC, OSTP, and OECD evidence. But the regulatory attitude has remained unchanged.

Consequently, the present regulatory paradigm in the United States, the European Union, New Zealand, and the Cartagena Protocol is an attitude of mistrust of science and scientists and an unwarranted, unsubstantiated, and non-empirical aversion to agricultural biotechnology. This attitude is fueled and promoted by a protest industry that thrives by spreading misinformation, promoting scientific ignorance, and creating fear. Regulatory agencies should not be allies of misinformation, ignorance, and fear.

Regulatory agencies should return to the paradigm set forth at the beginning of the biotechnological era. Regulatory agencies should adopt a paradigm of confidence in science and scientists, and an openness to agricultural biotechnology rooted in the biological sciences and the favorable empirical results of biotechnology in farmers' fields, industrial enzymes, and medicines. Regulatory agencies must adopt this benevolent paradigm, not only for rDNA breeding but also for the newer breeding techniques. Without this paradigm change, rDNA breeding will continue to be impaired, rather than stimulated. Without this paradigm change, newer breeding techniques likely will be imprisoned in laboratories and exiled from agriculture.

Most importantly, the authors are profoundly concerned that, without a paradigm change, poor and vulnerable populations will not have access to genetic-engineering technologies to enable them to raise their standards of living, improve their health and protect their environments (PAS, 2009). For good or ill, regulatory paradigms matter in the real world.

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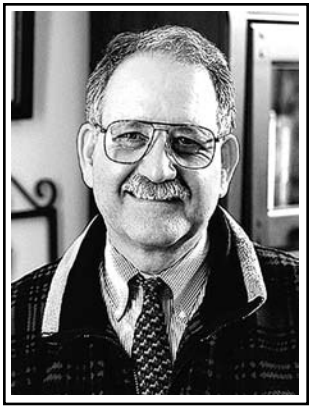

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